Emergence of Antimicrobial-Resistant Shigellosis in Oregon

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Ampicillin and trimethoprim-sulfamethoxazole (TMP-SMZ) are currently considered acceptable empirical therapy for shigellosis in developed countries. However, there are few recently reported studies on antimicrobial resistance among shigellae isolated in the United States. We examined the epidemiology of shigellosis and the antimicrobial susceptibility of Shigella species isolated in Oregon from July 1995 through June 1998. Of 430 isolates, 410 were identified to the species level: Shigella sonnei accounted for 55% of isolates, and Shigella flexneri, for 40%. The overall annual incidence of shigellosis was 4.4 cases per 100,000 population. Children aged <5 years (annual incidence, 19.6 cases per 100,000 population) and Hispanics (annual incidence, 28.4 cases per 100,000 population) were at highest risk. Of 369 isolates tested, 59% were resistant to TMP-SMZ, 63% were resistant to ampicillin, 1% were resistant to cefixime, and 0.3% were resistant to nalidixic acid; none of the isolates were resistant to ciprofloxacin. Thirteen percent of the isolates had multidrug resistance to ampicillin, chloramphenicol, streptomycin, sulfoxazole, and tetracycline. Infections due to multidrug-resistant shigellae are endemic in Oregon. Neither ampicillin nor TMP-SMZ should be considered appropriate empirical therapy for shigellosis any longer; when antibiotics are indicated, a quinolone or cefixime should be used.

Antimicrobial therapy has been recommended for patients with shigellosis because it can limit both the clinical course of illness and the duration of fecal excretion of the causative organism [1]. Although other countries have reported high rates of resistance of Shigella species to trimethoprim-sulfamethoxazole (TMP-SMZ) and other antimicrobial agents [2–11], previously reported data have indicated low levels of resistance in the United States; for example, only 7% of Shigella isolates in the United States were resistant to TMP-SMZ in 1985–1986 [12]. As a consequence, TMP-SMZ continues to be endorsed for the treatment of shigellosis in this country [1]. 13–16]. Given the contribution of imported cases to the incidence of shigellosis in the United States and the ability of Shigella to develop resistance rapidly after the introduction of new antibiotics, it is plausible that antimicrobial resistance patterns for Shigella isolates in the United States have changed since they were last examined [3, 8, 11, 12].

We investigated the epidemiology of shigellosis and the antimicrobial susceptibility of Shigella species isolated from July 1995 through June 1998 in Oregon, a northwestern state with a population of 3.2 million in 1997. Our findings indicate that multidrug resistance has not only emerged but has become common and suggest that our approach to empirical therapy for shigellosis needs to be reconsidered.

Methods

Case ascertainment. Shigellosis is reportable in Oregon both by clinicians and by microbiology laboratories. Clinicians are required to report cases and suspected cases within 1 working day. Working with the Foodborne Illness Active Surveillance Network (FoodNet, which is a cooperative agreement with the US Department of Agriculture, the US Food and Drug Administration, and the Centers for Disease Control and Prevention, and is part of the Emerging Infections Program), we conducted active surveillance for cases of shigellosis through regular review of records at all Oregon clinical microbiology laboratories. We defined a case as isolation of Shigella from the feces of an Oregon resident for whom the onset of illness (or, in the absence of clinical illness, date of specimen collection) was during the period 1 July 1995 to 30 June 1998. Local public health nurses routinely interview case subjects by using standard surveillance forms and collect information regarding demographics, possible sources of infection, and outcome; these data for our case subjects were forwarded to the Oregon Health Division (Portland).

Laboratory evaluation. In addition to reporting cases of infection, Oregon microbiology laboratories are required either to report species and serotypes of Shigella isolates or to forward them to the Oregon State Public Health Laboratory (Portland, OR) for typing. Confirmation of Shigella at the Oregon State Public Health Laboratory was done by means of standard biochemical methods, and serological grouping was done by slide agglutination testing.
with use of specific antisera (Denka Seiken, Tokyo) [17]. Each isolate was tested for susceptibility to ampicillin, cefixime, cephalothin, chloramphenicol, ciprofloxacin, gentamicin, nalidixic acid, nitrofurantoin, sulfisoxazole, trimethoprim, and TMP-SMZ (Difco Laboratories, Detroit) by use of the Kirby-Bauer disk diffusion method [18]. Isolates were also tested for resistance to tetracyclines: strains collected from 1 July 1995 through 30 June 1996 were tested for resistance to tetracycline, and strains collected later were tested for resistance to doxycycline. Isolates found to be multidrug-resistant to ampicillin, chloramphenicol, sulfa drugs, and tetracyclines were also tested for resistance to streptomycin. Quality control strains used for susceptibility testing were Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853, and Staphylococcus aureus ATCC 25923.

Data analysis. Age- and race- or ethnicity-specific incidences of shigellosis were calculated with use of denominators from 1997 Oregon population estimates [19]. Approximately 87% of Oregon’s population are non-Hispanic white, 4% are Hispanic, 3% are Asian, 2% are black, and 1% is Native American. Only 22 cases occurred in nonwhites, but 162 occurred in persons of Hispanic ethnicity; analysis by race and ethnicity was therefore limited to comparison of Hispanics with non-Hispanics. Because our analysis did not cover 3 calendar years, we defined 3 “study years” as follows: study year 1, 1 July 1995 through 30 June 1996; study year 2, 1 July 1996 through 30 June 1997; and study year 3, 1 July 1997 through 30 June 1998.

Results

Descriptive epidemiology. During the study period, 430 culture-confirmed cases of shigellosis were reported to the Oregon Health Division: study year 1, 140; study year 2, 113; and study year 3, 177. Of these cases, 125 (29%) occurred in children aged <5 years; 235 (55%) of the case subjects were female. The overall annual incidence of reported shigellosis in Oregon was 4.4 cases per 100,000 population. The annual incidence among children aged <5 years was 19.6 cases per 100,000 population, compared with 3.4 cases per 100,000 population among those aged ≥5 years. Age-specific incidences were similar for males and females. Four hundred ten (95%) of the isolates were identified to the species level; of these, 226 (55%) were Shigella sonnei, 166 (40%) were Shigella flexneri, 12 (3%) were Shigella boydii, and 6 (1%) were Shigella dysenteriae. Fifty case subjects (12%) were hospitalized, and 2 (0.5%) developed the hemolytic-uremic syndrome. One (0.2%) died; he was a 2-year-old boy infected with S. flexneri type 6.

Ethnicity was known for 379 (88%) of the case subjects; 162 (43%) of these were Hispanic, and 217 (57%) were non-Hispanic. The overall annual incidence among Hispanics was 12 times higher than that among non-Hispanics (28.4 vs. 2.4 cases per 100,000 population). S. flexneri was the most common species isolated from Hispanics (85 [55%] of 155 isolates identified to the species level), whereas S. sonnei was the most common species isolated from non-Hispanics (142 [68%] of 209 isolates identified to the species level). However, incidences of both S. flexneri infection and S. sonnei infection were much higher among Hispanics than among non-Hispanics. The risk of S. flexneri infection and the risk of S. sonnei infection for His-

![Figure 1](https://academic.oup.com/cid/article-abstract/30/3/515/600050/516)
Antimicrobial resistance. The Oregon State Public Health Laboratory received or identified isolates from 393 shigellosis cases reported during the study period; of these 393 isolates, 369 (86% of the 430 isolates from the reported cases) were viable for antimicrobial susceptibility testing. Age, sex, ethnicity, and infecting species were similar for the group of subjects whose isolates were tested for antimicrobial susceptibility and for the subjects whose isolates were not tested (data not shown); however, isolates from study year 3 were more likely to be tested (92%) than were those from study years 2 and 1 (84% and 79%, respectively).

Overall, 216 (59%) of the isolates tested were resistant to TMP-SMZ, 234 (63%) were resistant to ampicillin, and 313 (85%) were resistant to tetracycline. Four isolates (1%) were resistant to cefixime, and 1 (0.3%) was resistant to nalidixic acid. None of the isolates were resistant to ciprofloxacin. Only 12 isolates (3%) were pan-susceptible. Resistance patterns changed little over the 3 years of the study, except that the rate of ampicillin resistance among S. sonnei isolates increased from 31% in study year 1 to 68% in study year 3 (figure 1).

Antimicrobial resistance varied by species (table 1). Notably, 81% of S. sonnei isolates, but only 29% of S. flexneri isolates, were resistant to TMP-SMZ; 72% of S. flexneri isolates, but only 1% of S. sonnei isolates, were resistant to chloramphenicol. Common patterns of multidrug resistance are shown in table 2. The most common pattern was resistance to both ampicillin and tetracycline, found for 215 (58%) of 369 isolates tested. One hundred thirty-two isolates (36%) were resistant to ampicillin, tetracycline, and TMP-SMZ. Forty-eight isolates (13%) were multidrug-resistant to ampicillin, chloramphenicol, streptomycin, sulfisoxazole, and tetracycline (ACSSuT). Multidrug resistance also varied significantly by species (table 2).

To determine whether demographic variables could predict resistance to ampicillin or TMP-SMZ, we analyzed susceptibility to these drugs by age, sex, and ethnicity. Susceptibility patterns were similar for male and female subjects and for the different age groups (data not shown). Hispanics were more frequently infected with strains resistant to ampicillin than were non-Hispanics (72% vs. 56%, respectively). This finding was chiefly due to the higher proportion of S. flexneri infections among Hispanics, because resistance to ampicillin among S. flexneri isolates varied little by the ethnicity of the patient: 58 (85%) of 68 isolates from Hispanics vs. 45 (79%) of 57 isolates from non-Hispanics were resistant to ampicillin. The rate of resistance to TMP-SMZ was similar among isolates from Hispanics and isolates from non-Hispanics (54% and 64%, respectively). For S. sonnei, 51 (93%) of 55 isolates from Hispanics vs. 102 (80%) of 127 isolates from non-Hispanics were resistant to TMP-SMZ. ACSSuT resistance was seen in 15% of S. sonnei isolates, but only 29% of S. flexneri isolates were resistant to TMP-SMZ.
of isolates from Hispanics and in 11% of isolates from non-Hispanics.

Discussion

To our knowledge, the rates of TMP-SMZ resistance, ampicillin resistance, and multidrug resistance that were found among Oregon *Shigella* isolates are the highest ever reported from a developed nation. When we compared our data with those from reports from other developed Western nations, Oregon *S. flexneri* strains were either similarly or more resistant to each antimicrobial agent tested, except for the sulfonamides (table 1) [12, 20–22]. Of note, although only 19% of *S. flexneri* strains from the United States during 1985–1986 were resistant to ampicillin [12], 82% of our *S. flexneri* strains (isolated during 1995–1998) were resistant to this agent, and the rate of resistance to ampicillin among our *S. sonnei* isolates was climbing. Recent reported data from other states are lacking, but we doubt that such increases in resistance rates are unique to Oregon.

With 63% of our isolates resistant to ampicillin and 59% resistant to TMP-SMZ, Oregon *Shigella* isolates resemble those reported from Brazil, Bangladesh, and Thailand [8, 9, 11]. It is estimated that about one-half of Oregon’s 190,000 Hispanics are migrant workers who travel regularly to Mexico and other Latin American countries; because multidrug resistance among *Shigella* is widely reported there, it is plausible that resistant clones were imported from these developing countries [8, 20, 23, 24]. The fact that higher levels of ampicillin resistance were seen in Oregon *S. flexneri* isolates before they appeared in Oregon *S. sonnei* isolates corroborates this hypothesis.

The ACSSuT resistance pattern found here represents the first report of this antibiogram for shigellae in the United States. This 5-drug resistance pattern has been described for isolates of *Salmonella* Typhimurium DT 104 [25, 26], as well as for *Shigella* species in Argentina, Bangladesh, Brazil, Burundi, Germany, Somalia, the United Kingdom, and Zambia [6–8, 20, 22, 23, 27, 28]. In *Salmonella* Typhimurium DT 104, the genes for ACSSuT resistance appear to be located on the bacterial chromosome [29]. A 98-MDa plasmid has been associated with transferable ACSSuT resistance in *Salmonella* Typhi [30]. A 35-MDa plasmid was found to be capable of transferring resistance to ampicillin, carbenicillin, streptomycin, sulfisoxazole, tetracycline, and TMP-SMZ between *S. flexneri* and *E. coli* [31]. In *S. flexneri*, a chromosomal gene cluster has been shown to account for resistance to ampicillin, chloramphenicol, tetracycline, and spectinomycin [23]. To our knowledge, however, no single gene cluster has been associated with the entire ACSSuT resistance pattern for shigellae; it may be that ACSSuT resistance represents a piecemeal accumulation of resistance genes [6, 32]. Investigations into the mechanisms of antimicrobial resistance among Oregon shigellae are under way.

Regardless of its origins and mechanisms, the widespread resistance that we found among *S. flexneri* and *S. sonnei* suggests that infections due to drug-resistant shigellae are now endemic in Oregon. Because isolation and antimicrobial susceptibility testing for shigellae take at least 2 days, antimicrobial agents must generally be selected empirically. Neither TMP-SMZ nor ampicillin can be considered appropriate empirical therapy any longer. Regrettably, a patient’s age, sex, and ethnicity do not provide useful clues as to whether a given *Shigella* isolate is likely to be susceptible to recommended antimicrobial agents.

Quinolones remain a good choice for empirical treatment of shigellosis in adults [33]. Nalidixic acid is effective [34] and approved in the United States for use as treatment of children aged ≥3 months, and 99.7% of our *Shigella* isolates were susceptible to it. The rate of resistance to nalidixic acid has been as high as 26% on American Indian reservations, but this rate declined when use of the drug was reduced (unpublished data, Richard E. Besser). Other quinolones are likely to be effective in treating shigellosis in children, but pediatric use is limited in the United States by concerns about chondrotoxicity and the lack of approval by the US Food and Drug Administration [35]. Previously reported data suggest, however, that quinolones are generally safe for treatment of children [35, 36]. Cefixime was effective against 99% of our isolates in vitro, but there is some dispute as to the clinical efficacy of this drug in treating shigellosis [37, 38].

Although treatment of shigellosis with appropriate antimicrobial therapy results in decreased duration of both symptoms and excretion of the organism [1, 2, 34], it is worth noting that many cases can be managed solely with rehydration and supportive care. It may therefore be reasonable to reserve antimicrobial agents for only the most severe cases [1, 34]. With resistance rates comparable with those described here, the best approach may be to eschew antimicrobial therapy for most cases of shigellosis and to reserve quinolones or cefixime for patients who have severe disease, immunocompromised patients, and patients for whom eliminating carriage is a public health priority.

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